IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/561,529
Confirmation No.:	9788
First-Named Inventor:	Fabrizio Samaritani
Filing Date:	December 20, 2005
Group Art Unit:	1647
Examiner:	Stoica, Elly-Gerald
Attorney Docket No.:	007541-000005
Title:	FREEZE-DRIED FSH/LH FORMULATIONS

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the Notice of Appeal received by the United States Patent Office on June 8, 2009 in connection with the above-indicated application, an Appeal Brief according to 37 CFR §41.37 is provided along with the requisite fee of $540.00 for a large entity.

The Commissioner is authorized to grant any further extensions of time and charge any deficiency or credit any overpayment to Deposit Account No. 23-3030, but not to include issue fees.

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I. REAL PARTY IN INTEREST

(37 CFR §41.37(c)(1)(i))

The real party in interest in this appeal is Ares Trading, S.A., which is the owner of the present application by written assignment recorded at reel/frame number 018196/0025.

II. RELATED APPEALS AND INTERFERENCES

(37 CFR §41.37(c)(1)(ii))

The applicants, the applicants' legal representative, and the assignee are unaware of any related appeals or interferences which will affect, be directly affected by, or have a bearing on the Appeal Board's decision in the present appeal.

III. STATUS OF CLAIMS

(37 CFR §41.37(c)(1)(iii))

A. TOTAL NUMBER OF CLAIMS IN APPLICATION

There are 12 total claims pending in the application. The claims pending in the application are 46-51 and 55-60.

B. STATUS OF ALL THE CLAIMS

1. Claims canceled: 1-45 and 52-54.
2. Claims withdrawn from consideration but not canceled: None.
3. Claims allowed: None.
4. Claims rejected: 46-51 and 55-60.
5. Claims objected to: None.

C. CLAIMS ON APPEAL

The claims on appeal are 46-51 and 55-60.

IV. STATUS OF AMENDMENTS

(37 CFR §41.37(c)(1)(iv))

The last amendments entered in the claims were contained in the Response to Final Office Action, which was electronically filed and received by the Patent Office on March 9, 2009. In that Response, claims 1-45 and 52-54 were shown as canceled, and claims 46, 50, 51, and 55-58 were amended. In the Advisory Action mailed on March 30, 2009, it was indicated that the claim amendments would be entered for purposes of appeal, and all of the pending claims 46-51 and 55-60 were rejected.

V. SUMMARY OF CLAIMED SUBJECT MATTER

(37 CFR §41.37(c)(1)(v))

The following summarization explains how each of the independent claims reads on one or more embodiments of the present application. In this summarization, all page and line numbers refer to the corresponding text of the present application. It should be appreciated that the below summaries are to be interpreted as merely nonlimiting examples - it being understood that all other embodiments upon which the claims read are also intended to be covered.

The present inventions relate generally to freeze dried formulations including follicle-stimulating hormone ("FSH") and luteinising hormone ("LH"). The formulations contain a surfactant, a stabilizer and tonicity agent, an antioxidant, and a buffer. A key aspect of the inventions is that the formulations have a limited number of ingredients, while having surprising stability. Also provided are articles of manufacture and methods for making such formulations.

A. Independent Claim 46 and Dependent Claims 47-49 and 60

Independent claim 46 sets forth a formulation that reads on one or more embodiments of the present application. Claim 46 pertains to a formulation consisting of FSH, LH, selected surfactants, selected stabilizer and tonicity agents, an antioxidant and a phosphate buffer. Referring to the disclosure, FSH and LH are described on pages 5-7. The surfactants are described at page 10, lines 10-24. The stabilizer and tonicity agents are discussed at page 8, lines 13-19 and page 13, lines 32-35. The antioxidants are described at page 13, lines 18-30. The phosphate buffers are discussed at page 8, line 21 to page 9, line 2 and at page 11, line 36 to page 12, line 15. A specific example of an embodiment of claim 46 is provided in the example beginning on page 16.

Table A is included to assist the Board in locating support for each claim element.

Table A

ELEMENTS OF CLAIMS 46-49 AND 60	LOCATION OF SUPPORTING TEXT IN THE APPLICATION
46. A freeze-dried formulation consisting of:	P. 1, ll. 4-6; p. 4, ll. 10-14
a follicle-stimulating hormone or a variant thereof,	P. 5, l. 23 - p. 6, l. 13
a luteinising hormone or a variant thereof,	P. 7, ll. 7-16
at least one surfactant selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, and polyoxyethylene (20) sorbitan monooleate,	P. 10, ll. 10-24

a stabilizer and tonicity agent selected from the group consisting of monosaccharides, disaccharides and sugar alcohols,	P. 8, ll. 13-19; p. 9, ll. 12-29; p. 13, ll. 32-35
an antioxidant, and	P. 13, ll. 18-30
a phosphate buffer.	P. 8, l. 21 - p. 9, l. 2; p. 11, l. 36 - p. 12, l. 15
47. The freeze-dried formulation of claim 46 consisting of	P. 1, ll. 4-6; p. 4, ll. 10-14
recombinant human follicle-stimulating hormone,	P. 6, ll. 15-31; p. 11, ll. 20-34
recombinant human luteinising hormone,	P. 7, ll. 18-20; p. 11, ll. 20-34
polyoxyethylene (20) sorbitan monolaurate,	P. 10, ll. 10-24
sucrose,	P. 8, ll. 13-19; p. 9, ll. 12-29; p. 13, ll. 32-35
methionine, and	P. 13, ll. 18-30
a phosphate-buffer.	P. 8, l. 21 - p. 9, l. 2; p. 11, l. 36 - p. 12, l. 15
48. The freeze-dried formulation according to claim 47 including	
0.1-10 µg/mg recombinant human follicle-stimulating hormone,	P. 10, ll. 26-31
0.1-3 µg/mg recombinant human luteinising hormone, and	P. 10, ll. 33 to p. 11, l. 2
0.001-0.1 mg/mg polyoxyethylene (20) sorbitan monolaurate, based on the weight of the formulation.	P. 20, ll. 10-19
49. The freeze-dried formulation according to claim 48 in which the relative weight amounts of the components comprise 12.0 µg of recombinant human follicle-stimulating hormone, 3.7 µg of recombinant human luteinising hormone, 30.0 mg of sucrose, 0.05 mg of polyoxyethylene (20) sorbitan monolaurate and 0.1 mg of methionine.	P. 16, ll. 20-28
60. The freeze-dried formulation of claim 46 in which the biological activity of the FSH and of the LH is well conserved after nine months of storage.	P. 7, l. 30 to p. 8, l. 4; p. 18, l. 11 to p. 19, l. 1

B. Independent Claim 50 and Dependent Claims 51 and 59

Independent claim 50 sets forth an article of manufacture that reads on one or more embodiments of the present application. Claim 50 pertains to a pair of containers - one including a freeze-dried formulation and the other containing a diluent. The freeze-dried formulation within the first container corresponds to the formulation of claim 47, and the example beginning on page 16 provides a specific embodiment of that formulation. See, in particular, page 16, lines 20-28. The provision of separate containers for the formulation and the diluent is described, for example, at page 13, lines 4-10.

Table B is included to assist the Board in locating support for each claim element.

Table B	
ELEMENTS OF CLAIMS 50, 51 AND 59	LOCATION OF SUPPORTING TEXT IN THE APPLICATION
50. An article of manufacture comprising:	P. 4, ll. 22-27
a first container	P. 9, ll. 4-10
filled with a freeze-dried formulation consisting of a recombinant, human follicle-stimulating hormone or a variant thereof, a recombinant, human luteinising hormone or a variant thereof, polyoxyethylene (20) sorbitan monolaurate, sucrose, methionine; and a phosphate buffer.; and	P. 4, ll. 22-26; p. 13, ll. 4-9
a second container that comprises a solvent for reconstitution.	P. 4, l. 27; p. 12, ll. 17-19; p. 13, ll. 9-10; p. 14, ll. 7-8
51. The article of manufacture according to claim 50,wherein the second container contains water for reconstitution.	P. 12, ll. 17-19
59. The article of manufacture of claim 50 in which the first container is filled with a freeze-dried formulation consisting of recombinant human follicle-stimulating hormone, recombinant human luteinising hormone, polyoxyethylene (20) sorbitan monolaurate, sucrose, methionine, and a phosphate-buffer.	P. 4, ll. 22-26; p. 13, ll. 4-9

C. Independent Claim 55 and Dependent claims 56-58

Independent claim 55 sets forth a method that reads on one or more embodiments of the present application. Claim 55 pertains to the making of the freeze-dried formulation of claim 46. Claims 56-58 provide methods relating to the manufacture of the formulations of claims 47-49. The provision of methods for the making of such formulations is described, for example, at page 14, line 25 to page 17, line 30.

Table C is included to assist the Board in locating support for each claim element.

Table C	
ELEMENTS OF CLAIMS 55-58	LOCATION OF SUPPORTING TEXT IN THE APPLICATION
55. A method for manufacturing a freeze-dried formulation comprising:	P. 4, ll. 15-20
forming a mixture consisting of a follicle-stimulating hormone or a variant thereof, a luteinising hormone or a variant thereof, at least one surfactant selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, and polyoxyethylene (20) sorbitan monooleate, a stabilizer and tonicity agent selected from the group consisting of monosaccharides, disaccharides and sugar alcohols, an antioxidant, and a phosphate buffer; and	P. 12, ll. 27-31; p. 14, ll. 25-31

subjecting the mixture to lyophilization.	P. 12, ll. 31-32; p. 14, ll. 25-31
56. The method according to claim 55, wherein the mixture consists of recombinant human follicle-stimulating hormone, recombinant human luteinising hormone, sucrose, polyoxyethylene (20) sorbitan monolaurate and methionine.	P. 16, ll. 20-28
57. The method according to claim 56, wherein the mixture consists of component amounts to yield a freeze-dried formulation containing 0.1-10 μg/mg recombinant human follicle-stimulating hormone,	P. 10, ll. 26-31
0.1-3 μg/mg recombinant human luteinising hormone, and	P. 10, ll. 33 to p. 11, l. 2
0.001-0.1 mg/mg polyoxyethylene (20) sorbitan monolaurate, based on the weight of the formulation.	P. 20, ll. 10-19
58. The method according to claim 57, wherein the mixture consists of component amounts to yield relative weight amounts of the components in the freeze-dried formulation comprising 12.0 μg of recombinant human follicle-stimulating hormone, 3.7 μg of recombinant human luteinising hormone, 30.0 mg of sucrose, 0.05 mg of polyoxyethylene (20) sorbitan monolaurate and 0.1 mg of methionine	P. 16, ll. 20-28

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(37 CFR § 41.37(c)(1)(vi))

A concise statement of each ground of rejection presented for review is provided below.

A. Whether claim 55 is unpatentable under 35 U.S.C. §102(b), as being anticipated by De Meere et al. (U. S. Patent No. 5,384,132).

B. Whether claims 46-49, 56-58 AND 60 are unpatentable under 35 U.S.C. §103(a) as being obvious over De Meere et al. (U. S. Patent No. 5,384,132) in view of Skrabanja et al. (EP 0 853 945, 07/22/1998).

C. Whether claims 50-54 AND 59 are unpatentable under 35 U.S.C. §103(a) as being obvious over De Meere et al. (U. S. Patent No. 5,384,132) in view of Skrabanja et al. (EP 0 853 945, 07/22/1998), and further in view of Franks et al. (WO/2000/067778, 11/16/2000).

VII. ARGUMENT

(37 CFR § 41.37(c)(1)(vii))

The contentions of the applicant and the bases for those contentions with respect to each ground of rejection are presented below.

Introduction

Claims 46-51 and 55-60 are pending in the case. All of the pending claims use the transitional term "consisting of". All of the claims relate to freeze-dried formulations ***consisting of*** follicle stimulating hormone ("FSH") and luteinising hormone ("LH"), and certain other components. Claims 46 and 55 specify FSH, LH, and a phosphate buffer, and generally identify a surfactant (polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate or polyoxyethylene (20) sorbitan monooleate), a stabilizer/tonicity agent (monosaccharides, disaccharides or sugar alcohols), and an antioxidant. The other claims also specify FSH, LH and a phosphate buffer, but more specifically identify polyoxyethylene (20) sorbitan monolaurate, sucrose and methionine as the additional components. Claims 47-51 and 56-59 require recombinant FSH ("rFSH") and recombinant LH ("rLH").

A key aspect of the inventions is that the formulations of FSH and LH have surprising, long-term stability essential for a practical product. There has been a long-standing recognition of the difficulty in preparing stable FSH, and particularly rFSH, formulations:

> "The stability of proteins in aqueous formulations is generally a problem in [sic] pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer [sic] times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods." Skrabanja, EP 0 853 945, page 2, lines 42-45.

See also DeMeere (US Patent No. 5,384,132), col. 1, lines 30-37 and col. 2, lines 53-58. Stability is even more problematic for formulations including both FSH and LH:

> "A need exists for a gonadotropin containing pharmaceutical preparation which is stable over a sufficiently long period of time for the product to be manufactured, shipped, and stored prior to use. The need is especially great for a stable preparation containing more than one gonadotropin." De Meere, 5,384,132, col. 1, lines 38-43.

In contrast, applicants have found that formulations according to the present claims provide surprising stability, even for rFSH and rLH formulations, and without the need for

additional stabilizers. In particular, the present invention avoids the use of a polycarboxylic acid, or salt thereof, as required by the cited art.

All of the claims have been rejected as unpatentable over U.S. Patent No. 5,384,132 to De Meere et al. ("De Meere") and European Patent Application No. EP 0 853 945 to Skrabanja et al. ("Skrabanja"). The primary references to De Meere and Skrabanja have overlapping disclosures, and both require the use of a polycarboxylic acid/salt to provide stability. These references are distinguishable on that basis, as the claims are directed to formulations which "consist of" various components - not including a polycarboxylic acid/salt. The claim rejections fail to address the fact that the cited references clearly teach the requirement of a polycarboxylic acid/salt to achieve stability.

A. Rejection under 35 U.S.C. §102(b), as being anticipated by De Meere et al. (U. S. Patent No. 5,384,132)

1. Claim 55

Claim 55 recites a method for manufacturing a freeze-dried formulation which involves the lyophilization of a mixture "consisting of" certain components. The invention of claim 55 is seen to not be anticipated by De Meere for the reasons set forth hereafter.

De Meere

As noted, De Meere described a "need" for stable, lyophilized FSH preparations. The solution provided by DeMeere is the use of the salts of dicarboxylic acids to stabilize the formulations:

> "Disclosed are lyophilized gonadotropin containing preparations containing a dicarboxylic acid salt stabilizer." De Meere, Abstract, lines 1-3.
>
> "Generally, the invention includes a gonadotropin containing lyophilized protein preparation which contains a ***dicarboxylic acid salt stabilizer***. . . . The preparation will contain a sufficient amount of dicarboxylic acid salt to stabilize the gonadotropin in its freeze-dried form for a desired time at a desired temperature." De Meere, col. 1, lines 46-56 (emphasis added).

De Meere further taught that formulations without the dicarboxylic acid salts were not stable. In Example I, De Meere described the preparation of two FSH samples with the difference (other than the concentration of the Tween 20) being that the first sample included sodium citrate and the second did not. The results indicated the instability of the FSH formulation in the absence of sodium citrate:

> "The first sample is stored for 3 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed little oligomer formation. The second sample, not containing sodium citrate, was stored for 6 months at 50°C., reconstituted with purified water, and analyzed by HPSEC. The resulting profile showed much more oligomer formation.
>
> The profile of the first sample showed no degradation products while the profile of the second sample showed ***almost exclusively oligomeric products***." De Meere, col. 6, lines 45-56 (emphasis added).

Similarly, FIG. 2 showed only a 40% recovery of activity of HCG after freeze-drying, and only a 5% recovery of activity after storage at 50°C, in the absence of a citrate salt.

De Meere thus specifically teaches the need for the dicarboxylic acid salts, e.g., sodium citrate, in order to stabilize the FSH/LH formulations. The formulations may also include other excipients, including non-reducing salts (e.g., sucrose) to increase the "collapse temperature", and anti-adsorption agents (e.g., Polysorbates) to prevent adsorbance of the protein to the container walls. The use of sodium biphosphate is also mentioned. But in each instance, sodium citrate or the like is included.

Given the teaching of De Meere to use a dicarboxylic acid salt to stabilize the disclosed FSH formulations, it can not be said that De Meere anticipates claim 55, which involves the preparation of lyophilized FSH preparations that do not include a dicarboxylic acid salt.

Failure to address the "consisting of" language

It is apparent that the "consisting of" term in claim 55 has not been properly addressed, but rather the claim has been treated as a "comprising" claim. At the time of the Final Action, claim 55 used the term "consisting essentially of" in terms of the components of the FSH mixture. In rejecting claim 55, the examiner indicated that "the claims are drawn to formulations that 'consist essentially of', which does not exclude other elements like citric acid." Final Action, p. 5, lines 1-2. The examiner went on to say that "If Applicant wants to specifically exclude the citric acid containing formulation [sic] should do so explicitly by choosing the limiting term **consisting of**." Final Action, p. 5, lines 17-19 (emphasis added). However, in entering the amendments of the Response to Final, which changed the wording of claim 55 from "consisting essentially of" to "consisting of", the examiner simply stated that "The argument [sic] raised by Applicant in the Remarks filed on 03/09/2009 are largely duplicative to the ones raised in the response to the non-final rejection and were responded [sic] in the final rejection."

Thus, after seemingly inviting the applicant to use the "consisting of" term to distinguish the presence of sodium citrate used by De Meere, the examiner never addressed this issue.

Neither the Final Action or the Advisory Action purports to explain how removal of the dicarboxylic acid/salt could amount simply to "adjusting" or "optimizing" the ingredients of De Meere when the reference clearly is based on its use.

B. Rejections under 35 U.S.C. §103(a) as being obvious over De Meere et al. (U. S. Patent No. 5,384,132) in view of Skrabanja et al. (EP 0 853 945, 07/22/1998)

1. Claims 46-49, 56-58 and 60

Each of claims 46-49, 56-58 and 60 use the limiting term "consisting of" when referencing the claimed freeze-dried formulations or methods of making. The inventions of these claims are seen to not be obvious over De Meere in view of Skrabanja for the reasons set forth hereafter.

Skrabanja

Skrabanja describes formulations including FSH, LH and/or other gonadotropins which utilize a polycarboxylic acid, or salt thereof, for stabilization. Skrabanja more specifically discloses the use of a thioether compound to improve the stability achieved with the polycarboxylic acid/salt:

> "The invention relates to a liquid gonadotropin-containing formulation which comprises a gonadotropin and ***stabilizing amounts of a polycarboxylic acid or a salt thereof*** and of a thioether compound. The gonadotropin-containing formulations of the invention have improved stability on prolonged storage in comparison with formulations in which the thioether compound is lacking." **Skrabanja**, page 3, lines 15-18 (emphasis added).

Given the teachings of Skrabanja, and of De Meere, to use a polycarboxylic acid salt to stabilize the disclosed FSH formulations, it can not be said that the combination of De Meere and Skrabanja makes obvious claims 46-49, 56-58 and 60, which involve lyophilized FSH preparations that do not include a polycarboxylic acid salt.

Failure to address the "consisting of" language

It is apparent that the "consisting of" term in claims 46-49, 56-58 and 60 has not been properly addressed, but rather these claims have been treated as "comprising" claims. At the time of the Final Action, claims 56-58 were not limited to "consisting of" language, but claims 46-49 and 60 were so limited. The examiner never addressed this limitation in the rejection.

However, by comparison, in rejecting claim 55, the examiner noted the "consisting essentially of" language and stated that the claims did "not exclude other elements like citric acid." Final Action, p. 5, lines 1-2. The examiner went on to say that "If Applicant wants to specifically exclude the citric acid containing formulation [sic] should do so explicitly by choosing the limiting term **consisting of**." Final Action, p. 5, lines 17-19 (emphasis added). However, in addressing claims 46-49 and 60, which already included such language, the examiner did not address the issue of whether the absence of a polycarboxylic acid salt from the claims was distinguishing over the cited references. The same failure occurred when claims 56-58 were amended to the "consisting of" form in the Response to Final, in response to which the examiner simply stated that "The argument [sic] raised by Applicant in the Remarks filed on 03/09/2009 are largely duplicative to the ones raised in the response to the non-final rejection and were responded [sic] in the final rejection." Thus, after seemingly inviting the applicant to use the "consisting of" term to distinguish the presence of polycarboxylic acid salts as used by De Meere and Skrabanja, the examiner never addressed this issue.

The Final Action did contain a general comment on modification of De Meere and Skrabanja as follows:

> "The level of skill in the art at the time that the invention was made was very high, since formulations containing gonadotropins were widely known and used at the time that the invention was made. **Adjusting** the actual quantities of the ingredient was therefore considered routine in the art. Therefore it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of De Meere et al. and Skrabanja et al. to **optimize** the quantities with a reasonable expectation of success. The motivation is always present for a person of ordinary skill in the art to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense." Final Action, p. 7, lines 12-21 (emphasis added).

However, the examiner provided no basis beyond these sweeping, generic comments to support either the statements or the conclusion.

To say that the level of skill was "very high" ignores the very reason for the claimed inventions. Gonadotropins were well known to be difficult to keep stable over time, as reported by De Meere and Skrabanja. There is no evidence in the record that stable, lyophilized FSH formulations were well known, except for these two references which both rely on the use of polycarboxylic acid salts - something which the present inventions do not use.

On top of this, the examiner states that it would have been "obvious . . . to optimize the quantities with a reasonable expectation of success." However, how could it be said that removing the polycarboxylic acid salt disclosed and claimed by each of De Meere and Skrabanja could be considered "adjusting the actual quantities" in a manner "routine in the art"? How could it be an obvious "optimization" to totally remove the polycarboxylic acid salt which is precisely what is reported by both De Meere and Skrabanja as providing the stability which they required?

Neither the Final Action or the Advisory Action purports to explain how removal of the polycarboxylic acid/salt could amount simply to "adjusting" or "optimizing" the ingredients of De Meere or Skrabanja when the references are clearly based on its use. The De Meere and Skrabanja references both focus on the difficulty in providing stable FSH formulations, and claim to have solved this problem by the use of a polycarboxylic acid, or salt thereof. For example, without this stabilizer, DeMeere obtained "almost exclusively oligomeric products." De Meere, col. 6, lines 45-56. It is factually insufficient to state that the present invention is simply adjusting or optimizing the ingredients in the prior art. Both De Meere and Skrabanja not only disclose the use of polycarboxylic acids, or salts thereof, but they both indicate that the use of such acids/salts is the basis for the stabilization of their formulations.

2. Claims 47-49 and 56-58

Claims 47-49 and 56-58 are directed to formulations which include recombinant, human FSH and LH. The significance and novelty of the present invention are even greater with respect to the formulations covered by those claims.

The cited art indicates that stability of highly pure, rFSH and rLH is even more difficult to accomplish. De Meere, for example, indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "Recently however, with the advent of more effective production and purification techniques, preparations of certain very pure gonadotropins are insufficiently stable. They degrade in a relatively short time, losing activity. In order to prevent or slow down this degradation, attempts were made to freeze-dry (lyophilize) the preparations. Lyophilization has only been partially successful however." De Meere, col. 1, lines 30-37.

> "FSH purified from natural sources is generally only partially purified. The impurities seem to act to stabilize it somewhat. With rFSH, however the impurities are not present, and thus the FSH is more susceptible to rapid degradation and freeze-drying losses." De Meere, col. 2, lines 53-58.

Skrabanja also indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "With recFSH, however the impurities are not present and thus the FSH, being present in comparatively low concentration on the basis of protein is more susceptible to rapid degradation." Page 3, lines 53-54.

For these claims to recombinant FSH, the unobviousness is more evident on this basis.

C. Rejections under 35 U.S.C. §103(a) as being obvious over De Meere et al. (U. S. Patent No. 5,384,132) in view of Skrabanja et al. (EP 0 853 945, 07/22/1998), and further in view of Franks et al. (WO/2000/067778, 11/16/2000).

1. Claims 50-51 and 59

Each of claims 50-51 and 59 use the limiting term "consisting of" when referencing the claimed articles of manufacture relating to containers including a freeze-dried formulation of FSH. The inventions of these claims are seen to not be obvious over De Meere in view of Skrabanja, taken further in view of Franks, for the reasons set forth hereafter. The contentions regarding De Meere and Skrabanja are addressed *supra*.

Franks

Franks is primarily cited for the proposition that formulations of gonadotropins are known to be provided in unit-dose or multi-dose containers, for example sealed ampoules and vials, and that they may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Applicant submits that Franks does not otherwise provide a teaching that would render the present claims obvious.

Failure to address the "consisting of" language

It is apparent that the "consisting of" term in claims 50-51 and 59 has not been properly addressed, but rather these claims have been treated as "comprising" claims. At the time of the Final Action, claims 50-51 and 59 were not limited to "consisting of" language. The examiner never addressed this limitation in the rejection. However, by comparison, in rejecting claim 55, the examiner noted the "consisting essentially of" language and stated that the claims did "not exclude other elements like citric acid." Final Action, p. 5, lines 1-2. The examiner went on to say that "If Applicant wants to specifically exclude the citric acid containing formulation [sic] should do so explicitly by choosing the limiting term **consisting of**." Final Action, p. 5, lines 17-

19 (emphasis added). The examiner did not address this claim language when claims 50-51 and 59 were amended to the "consisting of" form in the Response to Final, in response to which the examiner simply stated that "The argument [sic] raised by Applicant in the Remarks filed on 03/09/2009 are largely duplicative to the ones raised in the response to the non-final rejection and were responded [sic] in the final rejection." Thus, after seemingly inviting the applicant to use the "consisting of" term to distinguish the presence of polycarboxylic acid salts as used by De Meere and Skrabanja, the examiner never addressed this issue.

The Final Action did contain a general comment on modification of De Meere and Skrabanja as follows:

> "The level of skill in the art at the time that the invention was made was very high, since formulations containing gonadotropins were widely known and used at the time that the invention was made. **Adjusting** the actual quantities of the ingredient was therefore considered routine in the art. Therefore it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of De Meere et al. and Skrabanja et al. to **optimize** the quantities with a reasonable expectation of success. The motivation is always present for a person of ordinary skill in the art to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense." Final Action, p. 7, lines 12-21 (emphasis added).

However, the examiner provided no basis beyond these sweeping, generic comments to support either the contained statements or the conclusion.

To say that the level of skill was "very high" ignores the very reason for the claimed inventions. Gonadotropins were well known to be difficult to keep stable over time, as reported by De Meere and Skrabanja. There is no evidence in the record that stable, lyophilized FSH formulations were well known, except for these two references which both rely on the use of polycarboxylic acid salts - something which the present inventions do not use.

On top of this, the examiner states that it would have been "obvious . . . to optimize the quantities with a reasonable expectation of success." However, how could it be said that removing the polycarboxylic acid salt disclosed and claimed by each of De Meere and Skrabanja could be considered "adjusting the actual quantities" in a manner "routine in the art"? How could it be an obvious "optimization" to totally remove the polycarboxylic acid salt which is precisely what is reported by both De Meere and Skrabanja as providing the stability which they required?

Neither the Final Action or the Advisory Action purports to explain how removal of the polycarboxylic acid/salt could amount simply to "adjusting" or "optimizing" the ingredients of De Meere or Skrabanja when the references clearly are based on its use. The De Meere and Skrabanja references both focus on the difficulty in providing stable FSH formulations, and claim to have solved this problem by the use of a polycarboxylic acid, or salt thereof. For example, without this stabilizer, DeMeere obtained "almost exclusively oligomeric products." De Meere, col. 6, lines 45-56. It is factually insufficient to state that the present invention is simply adjusting or optimizing the ingredients in the prior art. Both De Meere and Skrabanja not only disclose the use of polycarboxylic acids, or salts thereof, but they both indicate that the use of such acids/salts is the basis for the stabilization of their formulations.

2. Claims 50-51 and 59

Claims 50-51 and 59 are directed to formulations which include recombinant, human FSH and LH. The significance and novelty of the present invention are even greater with respect to the formulations covered by those claims.

The cited art indicates that stability of highly pure, rFSH and rLH is even more difficult to accomplish. DeMeere, for example, indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "Recently however, with the advent of more effective production and purification techniques, preparations of certain very pure gonadotropins are insufficiently stable. They degrade in a relatively short time, losing activity. In order to prevent or slow down this degradation, attempts were made to freeze-dry (lyophilize) the preparations. Lyophilization has only been partially successful however." De Meere, col. 1, lines 30-37.

> "FSH purified from natural sources is generally only partially purified. The impurities seem to act to stabilize it somewhat. With rFSH, however the impurities are not present, and thus the FSH is more susceptible to rapid degradation and freeze-drying losses." De Meere, col. 2, lines 53-58.

Skrabanja also indicates that stability is a particular problem for formulations including highly pure gonadotropins:

> "With recFSH, however the impurities are not present and thus the FSH, being present in comparatively low concentration on the basis of protein is more susceptible to rapid degradation." Page 3, lines 53-54.

For these claims to recombinant FSH, the unobviousness is more evident on this basis.

VIII. APPENDIX OF CLAIMS

(37 CFR § 41.37(c)(1)(viii))

The text of the claims involved in the appeal are:

46. A freeze-dried formulation consisting of:

a follicle-stimulating hormone or a variant thereof, a luteinising hormone or a variant thereof, at least one surfactant selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, and polyoxyethylene (20) sorbitan monooleate, a stabilizer and tonicity agent selected from the group consisting of monosaccharides, disaccharides and sugar alcohols, an antioxidant, and a phosphate buffer.

47. The freeze-dried formulation of claim 46 consisting of recombinant human follicle-stimulating hormone, recombinant human luteinising hormone, polyoxyethylene (20) sorbitan monolaurate, sucrose, methionine, and a phosphate-buffer.

48. The freeze-dried formulation according to claim 47 including: 0.1-10 μg/mg recombinant human follicle-stimulating hormone, 0.1-3 μg/mg recombinant human luteinising hormone, and 0.001-0.1 mg/mg polyoxyethylene (20) sorbitan monolaurate, based on the weight of the formulation.

49. The freeze-dried formulation according to claim 48 in which the relative weight amounts of the components comprise 12.0 μg of recombinant human follicle-stimulating hormone, 3.7 μg of recombinant human luteinising hormone, 30.0 mg of sucrose, 0.05 mg of polyoxyethylene (20) sorbitan monolaurate and 0.1 mg of methionine.

50. An article of manufacture comprising:

a first container filled with a freeze-dried formulation consisting of a recombinant, human follicle-stimulating hormone or a variant thereof, a recombinant, human luteinising hormone or a variant thereof, polyoxyethylene (20) sorbitan monolaurate, sucrose, methionine; and a phosphate buffer.; and

a second container that comprises a solvent for reconstitution.

51. The article of manufacture according to claim 50,wherein the second container contains water for reconstitution.

55. A method for manufacturing a freeze-dried formulation comprising:

forming a mixture consisting of a follicle-stimulating hormone or a variant thereof, a luteinising hormone or a variant thereof, at least one surfactant selected from

the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, and polyoxyethylene (20) sorbitan monooleate, a stabilizer and tonicity agent selected from the group consisting of monosaccharides, disaccharides and sugar alcohols, an antioxidant, and a phosphate buffer; and

subjecting the mixture to lyophilization.

56. The method according to claim 55, wherein the mixture consists of recombinant human follicle-stimulating hormone, recombinant human luteinising hormone, sucrose, polyoxyethylene (20) sorbitan monolaurate and methionine.

57. The method according to claim 56, wherein the mixture consists of component amounts to yield a freeze-dried formulation containing 0.1-10 μg/mg recombinant human follicle-stimulating hormone, 0.1-3 μg/mg recombinant human luteinising hormone, and 0.001-0.1 mg/mg polyoxyethylene (20) sorbitan monolaurate, based on the weight of the formulation.

58. The method according to claim 57, wherein the mixture consists of component amounts to yield relative weight amounts of the components in the freeze-dried formulation comprising 12.0 μg of recombinant human follicle-stimulating hormone, 3.7 μg of recombinant human luteinising hormone, 30.0 mg of sucrose, 0.05 mg of polyoxyethylene (20) sorbitan monolaurate and 0.1 mg of methionine.

59. The article of manufacture of claim 50 in which the first container is filled with a freeze-dried formulation consisting of recombinant human follicle-stimulating hormone, recombinant human luteinising hormone, polyoxyethylene (20) sorbitan monolaurate, sucrose, methionine, and a phosphate-buffer.

60. The freeze-dried formulation of claim 46 in which the biological activity of the FSH and of the LH is well conserved after nine months of storage.

IX. EVIDENCE APPENDIX

(37 CFR § 41.37(c)(1)(ix))

None.

X. RELATED PROCEEDINGS APPENDIX

(37 CFR § 41.37(c)(1)(x))

None.

Conclusion

It is respectfully requested that the bases for the final rejections of the pending claims be reviewed. If there are any questions or comments that would speed the prosecution, the Office is requested to contact the undersigned by telephone to quickly resolve any issues.

Respectfully submitted,

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